WEST Search History

DATE: Monday, September 29, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L7	l1 and probucol.ab.	28	L7
L6	l1 and probucol.ab	0	L6
L5	l1 same (clearance$1 or releas$3)	6	L5
L4	l1 and (clearance$1 or releas$3)	158	L4
L3	l1 and (monosuccinic ester$8)	0	L3
L2	l1 and (monosuccinic ester$8)	0	L2
L1	probucol same (lipoprotein$1 or lipid$)	269	L1

END OF SEARCH HISTORY

L7: Entry 2 of 28 File: USPT Sep 19, 2000

DOCUMENT-IDENTIFIER: US 6121319 A
TITLE: Monoesters of probucol for the treatment of cardiovascular and inflammatory disease

Abstract Text (1):
This invention is a method and composition for the inhibition of VCAM-1, and in particular for the treatment of cardiovascular or inflammatory disease, including atherosclerosis, that includes the administration of an effective amount of an ester of probucol.

Brief Summary Text (9):
Evidence suggests that the atherogenic effects of low density lipoprotein (LDL) may be in part mediated through its oxidative modification. Probucol has been shown to possess potent antioxidant properties and to block oxidative modification of LDL. Consistent with these findings, probucol has been shown to actually slow the progression of atherosclerosis in LDL receptor-deficient rabbits as discussed in Carew et al. Proc. Natl. Acad. Sci. U.S.A. 84:7725-7729 (1987). Most likely, probucol is effective because it is highly lipid soluble and is transported by lipoproteins, thus protecting them against oxidative damage.

Brief Summary Text (11):
Today, probucol is used primarily to lower serum cholesterol levels in hypercholesterolemic patients. Probucol is commonly administered in the form of tablets available under the trademark Lorelco.TM.. Unfortunately, probucol is almost insoluble in water and therefore cannot be injected intravenously. In fact, probucol is difficult for cells to absorb in vitro because of its poor miscibility in buffers and media for cell culture. Solid probucol is poorly absorbed into the blood, and is excreted in substantially unchanged form. Further, the tablet form of probucol is absorbed at significantly different rates and in different amounts by different patients. In one study (Heeg et al., Plasma Levels of Probucol in Man After Single and Repeated Oral Doses, La Nouvelle Presse Medicale, 9:2990-2994 (1980)), peak levels of probucol in sera were found to differ by as much as a factor of 20 from patient to patient. In another study, Kazuya et al. J. Lipid Res. 32; 197-204 (1991) observed an incorporation of less than about 1 .mu.g of probucol/10.sup.6 cells when endothelial cells are incubated for 24 h with 50 .mu.M probucol.

Drawing Description Text (6):
FIG. 5 is a bar chart graph of the effect of the monosuccinic acid ester of probucol and probucol on the cholesterol level in plasma of lipid-fed rabbits.

Drawing Description Text (9):
FIG. 8 is a bar chart graph of the effect of the monosuccinic acid ester of probucol on total cholesterol, LDLc, VLDLc, ILDLc, HDLc, and TG in lipid-fed rabbits after six weeks.

Drawing Description Text (10):
FIG. 9 is a graph of the percent aortic surface area covered by lesions in untreated lipid-fed rabbits and those treated with the monosuccinic acid ester of probucol.

Detailed Description Text (33):
Effect of Monosuccinic Acid Ester of Probucol on Cholesterol in Plasma of Lipid-fed Rabbits.

Detailed Description Text (34):
FIG. 5 is a bar chart graph of the effect of the monosuccinic acid ester of probucol and probucol on the total cholesterol and lipoprotein cholesterol levels in the plasma of lipid-fed rabbits. Rabbits were fed high-fat chow (0.5% cholesterol and 3% coconut oil) containing 0.5% wt/wt MSE or probucol for three weeks. Control animals were fed the same chow without drug added. Lipoprotein fractions were separated from whole plasma by fast phase liquid chromatography and analyzed for cholesterol content. MSE resulted in a statistically significant reduction in all lipoprotein fractions, and probucol only HDL cholesterol ($p<0.05$).

Detailed Description Text (37):
MSE or probucol were administered to rabbits in high-fat chow (0.5% cholesterol and 3% coconut oil) at a concentration of 0.5% wt/wt for three weeks. The drugs were extracted from plasma with ether and analyzed by high pressure liquid chromatography. As indicated, the level of probucol and MSE were similar, even though , as shown in the examples above, the compounds had a significantly different effect on the plasma cholesterol and lipoprotein levels.

Detailed Description Text (43):
New Zealand white rabbits were fed high fat high cholesterol (0.5%) diets alone or together with 0.5 weight per weight (approximately 150 mg/kg/day) either AGE-3 or probucol for six weeks. FIG. 8 is a bar chart graph of the effect of the monosuccinic acid ester of probucol on total cholesterol, LDLc VLDLc, ILDLc, HDLc, and triglycerides (TG) in lipid-fed rabbits after six weeks. After six weeks, lipoprotein fractions were separated from whole plasma by fast phase liquid chromatography, and analyzed for cholesterol and triglyceride content. As indicated in Example 8, total cholesterol, as well as the cholesterol in VLDL and IDL were lowered more by treatment with AGE-3 than with probucol.

Detailed Description Text (46):
The rabbits described in Example 8 were sacrificed and aortas obtained. The aortas were stained with sudan-4 and the extent of staining analyzed. FIG. 9 is a graph of the percent aortic surface area covered by lesions in MSE treated and untreated lipid-fed rabbits. The aortas of the rabbits that received AGE-3 had much less staining, indicating decreased atherosclerosis in those treated with the monosuccinic acid ester of probucol.

Detailed Description Text (74):
The active compound or pharmaceutically acceptable derivatives or salts thereof can also be administered with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatories, or antiviral compounds. The active compounds can be administered with lipid lowering agents such as probucol and nicotinic acid; platelet aggregation inhibitors such as aspirin; antithrombotic agents such as coumadin; calcium channel blockers such as varapamil, diltiazem, and nifedipine; angiotensin converting enzyme (ACE) inhibitors such as captopril and enalopril, and .beta.-blockers such as propanalol, terbutalol, and labetalol. The compounds can also be administered in combination with nonsteroidal antiinflammatories such as ibuprofen, indomethacin, aspirin, fenoprofen, mefenamic acid, flufenamic acid, sulindac. The compound can also be administered with corticosteriods.

Other Reference Publication (13):
Parthasarathy, S. et al., Probucol Inhibits Oxifative Modification of Low Density Lipoprotein, J. Clin. Invest., 77 641-644 (1986).

CLAIMS:

8. The method of claim 6, further comprising administering the monoester of probucol in combination with another cardiovascular agent selected from the group consisting of lipid lowering agent, platelet aggregation inhibitors, antithrombotic agents, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors and .beta.-blockers.

L1: Entry 2 of 269 File: USPT Sep 9, 2003

DOCUMENT-IDENTIFIER: US 6617352 B2
TITLE: Compounds and methods for the inhibition of the expression of VCAM-1

Brief Summary Text (30):
Evidence suggests that the atherogenic effects of low density lipoprotein (LDL) may be in part mediated through its oxidative modification. Probucol has been shown to possess potent antioxidant properties and to block oxidative modification of LDL. Consistent with these findings, probucol has been shown to actually slow the progression of atherosclerosis in LDL receptor-deficient rabbits as discussed in Carew et al. Proc. Natl. Acad. Sci. U.S.A. 84:7725-7729 (1987). Most likely, probucol is effective because it is highly lipid soluble and is transported by lipoproteins, thus protecting them against oxidative damage.

Brief Summary Text (32):
Probucol is used primarily to lower serum cholesterol levels in hypercholesterolemic patients. Probucol is commonly administered in the form of tablets available under the trademark Lorelco.TM.. Unfortunately, probucol is almost insoluble in water and therefore cannot be injected intravenously. In fact, probucol is difficult for cells to absorb in vitro because of its poor miscibility in buffers and media for cell culture. Solid probucol is poorly absorbed into the blood, and is excreted in substantially unchanged form. Further, the tablet form of probucol is absorbed at significantly different rates and in different amounts by different patients. In one study (Heeg, et al., Plasma Levels of Probucol in Man After Singleand Repeated Oral Doses, La Nouvelle Presse Medicale, 9:2290-2294 (1980)), peak levels of probucol in sera were found to differ as much as a factor of 20 from patient to patient. In another study, Kazuyza et al., J. Lipid Res. 32; 197-204 (1991) observed an incorporation of less than about 1 .mu.g of probucol/10.sup.6 cells when endothelial cells are incubated for 24 h with 50 .mu.M probucol.

Detailed Description Text (311):
The compound can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action. The active compounds can be administered in conjunction with other medications used in the treatment of cardiovascular disease, including lipid lowering agents such as probucol and nicotinic acid; platelet aggregation inhibitors such as aspirin; antithrombotic agents such as coumadin; calcium channel blockers such as varapamil, diltiazem, and nifedipine; angiotensin converting enzyme (ACE) inhibitors such as captopril and enalopril, and .beta.-blockers such as propanalol, terbutalol, and labetalol. The compounds can also be administered in combination with nonsteroidal antiinflammatories such as ibuprofen, indomethacin, fenoprofen, mefenamic acid, flufenamic acid, sulindac. The compound can also be administered with corticosteriods.

Other Reference Publication (9):
Fruebis et al., A Comparison of the Antiatherogenic Effects of Probucol and of a Structural Analogue of Probucol in Low Density Lipoprotein Receptor-deficient Rabbits, J. Clin. Invest., vol. 94, Jul. 1994, pp. 392-398.

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L1: Entry 8 of 269 File: USPT Aug 5, 2003

DOCUMENT-IDENTIFIER: US 6602914 B2
TITLE: Compounds and methods for the inhibition of the expression of VCAM-1

Brief Summary Text (29):
Evidence suggests that the atherogenic effects of low density lipoprotein (LDL) may be in part mediated through its oxidative modification. Probucol has been shown to possess potent antioxidant properties and to block oxidative modification of LDL. Consistent with these findings, probucol has been shown to actually slow the progression of atherosclerosis in LDL receptor-deficient rabbits as discussed in Carew et al. Proc. Natl. Acad. Sci. U.S.A. 84:7725-7729 (1987). Most likely, probucol is effective because it is highly lipid soluble and is transported by lipoproteins, thus protecting them against oxidative damage.

Brief Summary Text (31):
Probucol is used primarily to lower serum cholesterol levels in hypercholesterolemic patients. Probucol is commonly administered in the form of tablets available under the trademark Lorelco.TM.. Unfortunately, probucol is almost insoluble in water and therefore cannot be injected intravenously. In fact, probucol is difficult for cells to absorb in vitro because of its poor miscibility in buffers and media for cell culture. Solid probucol is poorly absorbed into the blood, and is excreted in substantially unchanged form. Further, the tablet form of probucol is absorbed at significantly different rates and in different amounts by different patients. In one study (Heeg et al., Plasma Levels of Probucol in Man After Single and Repeated Oral Doses, La Nouvelle Presse Medicale, 9:2990-2994 (1980)), peak levels of probucol in sera were found to differ by as much as a factor of 20 from patient to patient. In another study, Kazuya et al. J. Lipid Res. 32; 197-204 (1991) observed an incorporation of less than about 1 .mu.g of probucol/10.sup.6 cells when endothelial cells are incubated for 24 h with 50 .mu.M probucol.

Detailed Description Text (303):
The compound can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action. The active compounds can be administered in conjunction with other medications used in the treatment of cardiovascular disease, including lipid lowering agents such as probucol and nicotinic acid; platelet aggregation inhibitors such as aspirin; antithrombotic agents such as coumadin; calcium channel blockers such as varapamil, diltiazem, and nifedipine; angiotensin converting enzyme (ACE) inhibitors such as captopril and enalopril, and .beta.-blockers such as propanalol, terbutalol, and labetalol. The compounds can also be administered in combination with nonsteroidal antiinflammatories such as ibuprofen, indomethacin, fenoprofen, mefenamic acid, flufenamic acid, sulindac. The compound can also be administered with corticosteriods.

Other Reference Publication (10):
Fruebis et al., A Comparison of the Antiatherogenic Effects of Probucol and of a Structural Analogue of Probucol in Low Density Lipoprotein Receptor-deficient Rabbits, J. Clin. Invest., vol. 94, Jul. 1994, pp. 392-398.

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L5: Entry 1 of 6 File: USPT Feb 25, 2003

DOCUMENT-IDENTIFIER: US 6524795 B1
TITLE: Diagnostics for cardiovascular disorders

Detailed Description Text (136):
Factors associated with the progression of atherosclerosis include Diabetes Mellitus, high blood pressure, Hypercholesterolemia, High lipoprotein-a, Obesity, and Smoking. Of these, the factors amenable to pharmacological intervention include: i) diabetes, ii) hypertension, and iii) dyslipidemias. Examples of lipid lowering drugs include: Anion exchange resins such as cholestyramine, colestipol; HMG CoA reductase inhibitors or (statins) such as simvastatin, pracastatin, cerivastatin, fluvastatin, atorvastatin, lovastatin; Fibrates such as fenofibrate, bezafibrate, gemfibrozil, clofibrate, ciprofibrate; Nicotinic acid and analogues: acipimox, nicofuranose; Probucol which increases non-receptor mediated LDL clearance and decreases LDL oxidation; Fish oils such as maxepa, Omacor; and Cholesterol absorption inhibitors such as pamaqueside, tiqueside.

L5: Entry 5 of 6 File: USPT Nov 16, 1993

DOCUMENT-IDENTIFIER: US 5262439 A
TITLE: Soluble analogs of probucol

Brief Summary Text (16):
In yet another aspect, the present invention provides a method for delivering a therapeutic amount of a probucol compound to a part of an animal that is susceptible to oxidation. The method involves administering a probucol compound ester of the present invention to the animal and then transporting it to the part of the animal being susceptible to oxidation. Finally, the water-soluble derivative is hydrolyzed to release free probucol compound to the part of the animal susceptible to oxidation. Preferably the probucol compound will be released into lipid-containing material in the part of the animal susceptible to oxidation.

Detailed Description Text (14):
Because the compositions of this invention are water-soluble, they may be transported in aqueous media such as buffers or plasma. Thus, when administered, as by intravenous injection, they are rapidly directed throughout the body to locations that are susceptible to oxidative damage. As these compositions hydrolyze to release free probucol or probucol analog, they are taken up in lipid-containing regions in the animal, including those regions susceptible to oxidation (e.g. plasma membranes and LDL). Cells such as neutrophils and monocytes that undergo rapid respiratory burst upon certain types of stimulation may produce lesser amounts of oxygen radicals when enriched with antioxidants in this manner. Thus leukocytes may generate less superoxide anion radicals when they take up and hydrolyze water-soluble probucol.

Detailed Description Text (31):
It was still necessary to consider the possibility that free probucol generated during the 3 hour incubation or generated by hydrolysis in the cell might find its way into the LDL particle and act as an antioxidant in the medium. Thus, endothelial cells were incubated with 25 nmol of .sup.14 C-labeled diglutaryl probucol for 3 hours and after washing fresh medium and LDL were added. The LDL recovered from the medium showed absence of oxidation but was readily modified upon a subsequent incubation in the presence of 5 .mu.M copper. However, when higher concentrations 50-200 nmol of diglutaryl probucol were incubated with endothelial cells, there was considerable release of free probucol into the medium (in a 24 hour incubation) even after several washings with medium containing lipoprotein-deficient medium. Nevertheless, after two subsequent incubations with LDL at 100 .mu.g/ml for 24 hours each, 30-45% of the incorporated radioactivity was still associated with the cells. It should be pointed out that in these experiments, more than 15 nmol of probucol was incorporated into the cells of which about 7 nmol were released into the medium during a 24 hour incubation with LDL. The LDL recovered from such incubations was resistant to modification upon a subsequent incubation with 5 .mu.M copper. Thus, cells enriched in probucol, also released the antioxidant into the medium which may offer additional protection against oxidation. The rate of release of probucol from cells was not followed in these studies.

Detailed Description Text (32):
While the presence of probucol in LDL clearly protects it to some extent against oxidative modification, by acting as a relatively nonspecific antioxidant within the LDL particle, the present results suggest an additional mode of action that may be relevant to the in vivo effects of probucol. While the rate of entrance of probucol

into cells in culture is slow, the cells of animals treated chronically with the drug may take up enough of it so that their metabolism is altered, most specifically, their ability to oxidatively modify LDL. Probucol has been reported to accumulate in several tissues at concentrations even higher than in plasma. Other studies have implicated lipoxygenases in the oxidative modification of LDL. It has been proposed that the lipoxygenases act initially on cell lipids to generate hydroperoxides of fatty acids which are then transferred to the LDL. Probucol within the cell might prevent the generation of such lipoperoxides either by acting directly on the lipoxygenase systems or by limiting propagation reactions within the cell membrane. Cells may also release stored probucol into the extracellular medium, thus limiting lipid peroxidation. These findings suggest still another strategy for inhibition of oxidative modification of LDL, i.e., the introduction of compounds into cells to inhibit their ability to induce LDL oxidation. The combination of an antioxidant within the LDL molecule and the presence of an inhibitor within the cells might be additive. Thus, the antiatherogenic effects of probucol may very well depend upon such a two-pronged mode of action.

CLAIMS:

13. A method of delivering a therapeutic amount of probucol or a probucol analog to part of an animal, said part being susceptible to oxidation, said method comprising the following steps:

administering a water-soluble ester of probucol or a probucol analog to said animal; and

hydrolyzing said ester to release free probucol or probucol analog, said hydrolyzing action occurring at the part of said animal susceptible to oxidation, wherein the free probucol or probucol analog is released into a lipid containing material.

L7: Entry 6 of 28 File: USPT Dec 4, 1990

DOCUMENT-IDENTIFIER: US 4975467 A
**** See image for Certificate of Correction ****
TITLE: Method of inhibiting interleukin-1 release and alleviating interleukin-1 mediated conditions

Abstract Text (1):
Methods useful for inhibiting the release of Interleukin-1 and for alleviating interleukin-1 mediated conditions, such as IL-1 mediated inflammation, comprising administration of an effective amount of an alkylidenedithiobis(substituted)phenol, preferably, 4,4'-(isopropylidenedithio(bis(2,6-di-tert-butyl) phenol, generically known as probucol.

Brief Summary Text (3):
The substituted alkylidenedithio-bis-(substituted)phenols used in the invention are compounds of the type disclosed in U.S. Pat. Nos. 3,576,883, 3,786,100, 3,862,332 and 3,897,500 and can be made by the methods disclosed in those patents. One of the alkylidenedithio-bis(substituted)phenols, 4,4'-(isopropylidenedithio)bis(2,6-di-tert-butyl) phenol), is known by the generic name "probucol", and is used as a hypocholesterolemic drug. Probucol is known to lower serum cholesterol, and to reduce both high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol. It has been shown to inhibit oxidative modification of LDL, an effect which has been hypothesized as possibly inhibiting atherogenesis. Naruszewicz et al., Journal of Lipid Research, Vol. 25, 1206 (1984); and Parthasarathy et al., J.Clin.Invest., Vol. 77, 641 (1985).

Brief Summary Text (18):
Although the compounds of the invention, and probucol in particular, are known to be capable of reducing cholesterol, as well as reducing LDL and HDL cholesterol and inhibiting oxidation of LDL cholesterol, it is not necessary for the purposes of the invention that the compounds be administered to an animal in need of the cholesterol-lowering, lipid lowering, or cholesterol oxidation-inhibiting properties of the compounds. Some of the compounds which have useful IL-1 release inhibiting properties have only slight or negligible cholesterol lowering activity. The compounds can be administered to a non-hypercholesterolemic mammal suffering from IL-1-mediated inflammation, with advantageous results in reduction or elimination of the inflammation, or the compounds can be administered to non-hypercholesterolemic animals to alleviate atherosclerotic lesion conditions.